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OPITZ G/BBB SYNDROME: CLINICAL COMPARISONS OF FAMILIES LINKED TO Xp22 AND 22q, AND A REVIEW OF THE LITERATURE

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Opitz G/BBB syndrome (OS) was first described in 1969 as two separate disorders, the G syndrome, and the BBB syndrome. Since that time, it has become apparent that the BBB and the G syndromes are in fact a single entity, now named the Opitz G/BBB syndrome. However, our recent molecular genetic mapping studies have shown that OS is an heterogeneous disorder, with loci at Xp22 and 22q.

To determine if there are any discernible phenotypic differences between the X-linked and the autosomal dominant forms of OS, we have conducted a clinical study of the families who participated in the linkage analysis. In addition, we compared the clinical findings in the study families with those who have been reported in the literature.

We found that anteverted nares and posterior pharyngeal cleft were seen only in X-linked families. However, all other manifestations of OS, such as hypertelorism, swallowing difficulties, hypospadias, and developmental delay, were seen in both groups. Therefore, while OS is heterogeneous, significant clinical overlap is present between the two groups, and it is presently impossible to assign a specific phenotype to the X-linked or the autosomal type of OS. Furthermore, we found that for individuals in our study families who carried the OS allele, the incidence of major abnormalities was lower than what is reported in the literature.

KEY WORDS: Opitz G/BBB syndrome, hypertelorism-hypospadias syndrome, X chromosome, chromosome 22, heterogeneity

INTRODUCTION

In recent years, molecular genetic research has provided a greater understanding of many clinically defined genetic syndromes. However, these findings have often produced unexpected results, forcing the clinical geneticist to revisit previously held notions about a disorder. Such

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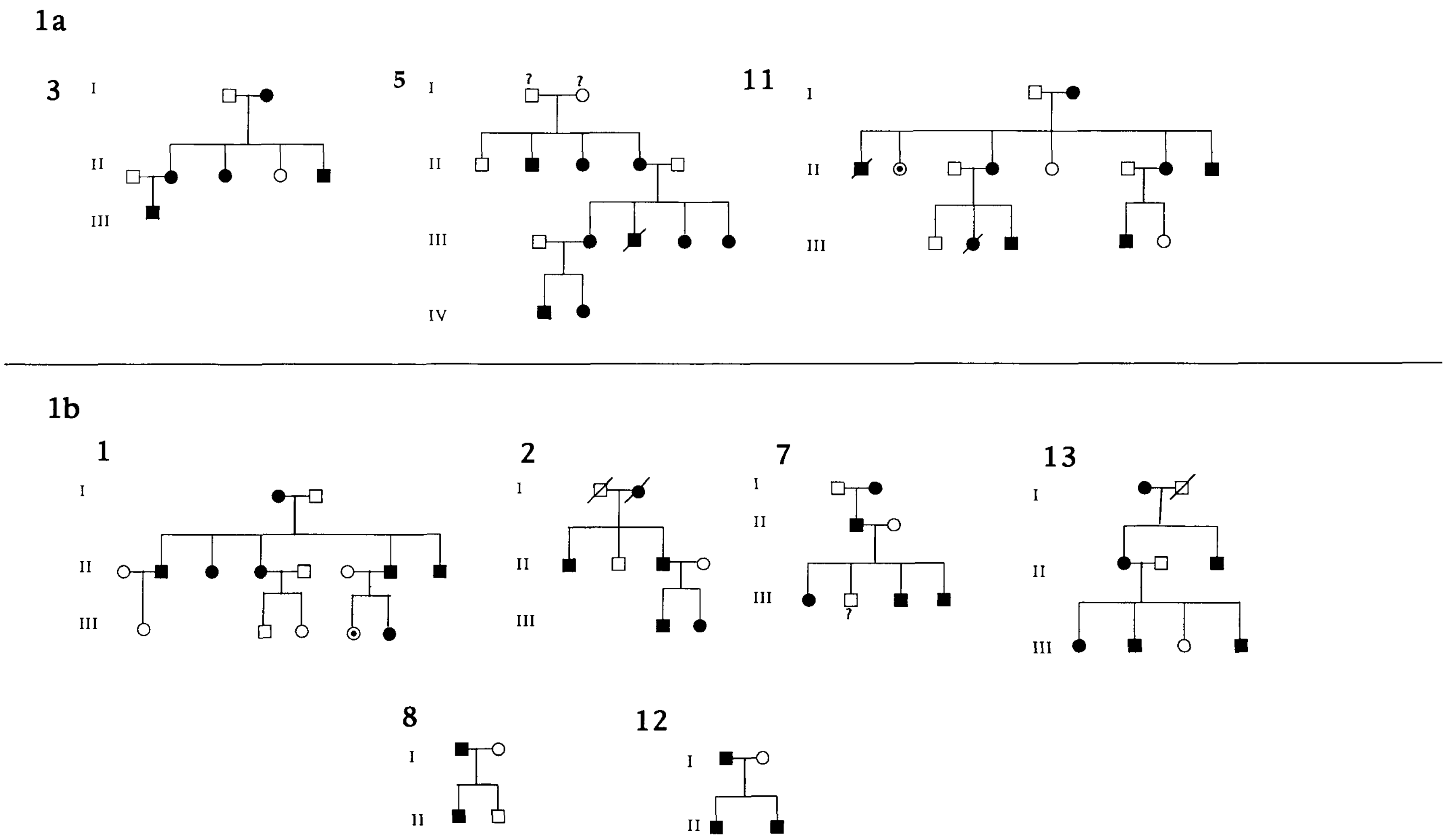

Figure 1. Pedigrees of the X-linked (1a) and 22-linked (1b) families; ⊙ signifies phenotypically normal individuals who inherited the chromosome with the Opitz syndrome gene; **?** signifies individuals in whom disease status could not be ascertained.

is now the case with the Opitz G/BBB syndrome (OS), as recent molecular genetic studies have shown it to be an heterogeneous disorder, with one locus at Xp22, and another at 22q [Robin et al., 1995]. This finding was supported by two recent case reports. First, a large kindred with the OS phenotype was shown to segregate with a pericentric inversion of the X chromosome with breakpoints at Xp22.3 and Xq26 [Verloes et al., 1995]. The breakpoint at Xp22.3 coincides with the map position found in three kindreds by Robin et al. [1995]. A second report documented that patients with findings of both OS and DiGeorge/ velocardiofacial syndrome (DG/VCF) had deletions in 22q11.2, [McDonald-McGinn et al., 1995].

In an effort to address this heterogeneity, we have initiated an ongoing study to determine if there are phenotypic distinctions between affected individuals in families linked to Xp22 (XLOS) and those linked to 22q (ADOS), and to ascertain what the range of manifestations is in individuals carrying the OS gene. In addition, we compared the clinical manifestations of the affected individuals in our study families with what has been reported previously in the literature. Here we report the results of these studies.

Figure 2. Individuals II-6 and 7, and III-4 and III-5 from family 1. III-5 is the proposita of that family, manifesting hypertelorism, cleft lip and palate, a laryngotracheal malformation, and conductive hearing loss. Her father, II-7, manifests hypertelorism. Her sister, III-4, is an unaffected carrier.

MATERIALS AND METHODS

Clinical information was reviewed from the 9 families who participated in the linkage analysis in which linkage to Xp22 or 22q could be determined [Robin et al., 1995]. Their pedigrees are shown in Fig. 1. Four families were published previously: families 1 (Figs. 2 and 3) [Allanson, 1988], 3 [Brooks et al., 1992], 7 [Guion-Almeida and Richieri-Costa, 1992], and 11, the original "G" family [Opitz et al., 1969a].

Figure 3. Individual II-8 from family 1, manifesting hypertelorism and a cleft lip and palate.

TABLE I. Comparison of Manifestations of Opitz BBBG Syndrome Among Cases Reported in the Literature (1), Cases Within Families with Male-to-Male Transmission (2), Cases in Families Found to be Linked to Xp22 (3) and 22q (4).

	1. Literature[a]		2. Literature[b]		3. Study: XLOS[c]		4. Study: ADOS[c]	
Manifestation	Males	Females	Males	Females	Males	Females	Males	Females
Hypertelorism/ telecanthus	93/101	56/60	14/14	3/3	9/9	10/12	15/15	9/10
Prominent forehead	29/42	11/16	3/8	-	7/8	4/12	11/13	7/9
Widow's peak	10/19	2/13	1/8	-	4/6	0/11	4/13	1/7
Broad nasal bridge	46/51	18/19	4/6	-	6/6	11/13	10/14	2/7
Anteverted nares	33/53	12/15	0/5	-	4/6	4/13	0/13	0/7
Cleft lip/palate	45/77	4/26	0/14	-	3/7	0/14	3/15	2/7
High arched palate	24/52	5/22	4/6	-	2/3	0/3	2/8	0/4
Grooved nasal tip	3	4	2/2	-	1	0	0	0
Flat philtrum	5/9	8/15	4/5	-	6/6	5/12	1/12	1/5
Minor anomalies of auricles	23/26	3/8	4/5	-	7/7	2/13	6/12	2/7
Laryngotracheal abnormality	21/49	13/23	6/9	-	3/4	1/8	2/13	1/7
Dysphagia/aspiration/GER	63/80	16/26	5/8	-	7/9	3/13	3/13	1/8
Congenital heart defect	17/44	7/21	2/6	-	1/8	0/13	1/16	0/9
Malrotation	4	0	-	-	0	0	1	0
Imperforate/ectopic anus	23/64	5/25	3/10	1/4	4/10	0/12	0/16	0/9
Hypospadias	73/97	-	9/13	-	9/10	-	5/16	-
Urinary tract anomalies	2/13	1/3	-	-	1/6	1/11	1/12	0/6
Cryptorchidism	15/52	-	1/6	-	1/8	-	1/14	-
Developmental delay	33/55	17/33	3/5	0/2	1/5	0/13	4/16	2/9
Agenesis of the corpus callosum/ other brain anomalies	11	0	0	0	0	0	3	1

[a] Baldellou et al., 1991; Bershof et al., 1992; Buckley et al., 1988; Cappa et al., 1987; Cavallo et al., 1988; Einfeld et al., 1987; Fryns et al., 1992; Guion-Almeida and Richieri-Costa, 1992; Hogdall et al., 1989; Howell and Smith, 1989; Kapoor and Rodgers, 1992; MacDonald et al., 1993; Opitz, 1987; Schrander et al., 1995; Stevens and Wilroy, 1988; Verloes et al., 1989; Williams and Frías, 1987; Wilson and Oliver, 1988; Young et al., 1988.

[b] All reports of families with male-to-male transmission: Funderburk and Stewart, 1978 (case 1); Farndon and Donnai, 1983, Chemke et al., 1984; Stoll et al., 1985; Tolmie et al., 1987 (family 1); Wilson and Oliver, 1988 (case 3).

[c] The total number represents all individuals who carry the affected allele, as determined by linkage study [Robin et al., 1995].

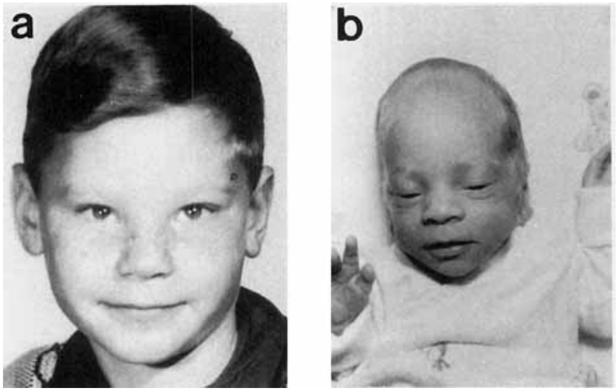

Figure 4a. Individual III-1 from family 2. He manifests hypertelorism, a broad and flat nasal bridge, high arched palate, and hypospadias. (4b) His father II-3 manifests hypertelorism, a broad and flat nasal bridge, and a thin upper lip with a smooth vermilion border and philtrum.

Additional information was gathered through examination of photographs and interviews with relatives.

The clinical findings in the remaining families (Figs. 4-7) have not been reported previously. Clinical data were provided by the referring geneticist, through the evaluation of photographs, and by telephone interviews. The data for the literature cases were derived from published reports and photographs. However, data were not included for patients with OS and a cytogenetic abnormality [Say and Carpenter, 1987; Christodolou et al., 1990; Leichtman et al., 1991; Verloes et al., 1995; Urioste et al., 1995]. As was done with the cases from this study, data from the literature cases were recorded as present or absent based on whether the anomaly was reported, or could be ascertained through the published photographs. If there was uncertainty, no entry was made for that manifestation.

RESULTS

Comparison of XLOS and ADOS

We compared the findings in affected individuals from families linked to Xp22 with those linked to 22q markers, and with the reported cases from the literature (Table I). The most consistent manifestation of the condition in both XLOS and ADOS groups was hypertelorism. Only three females, two from the XLOS families (II-3, from family 3, and II-2, from family 11), and one from the ADOS families (II-4, from family 1) were apparently not hyperteloric. One of these individuals (II-3 from family 3) had a urinary tract anomaly and abnormal urethra, and is therefore considered clinically affected. However, the other 2 individuals had no manifestations of OS but carried the OS allele. Thus, our molecular linkage study confirms non-penetrance in OS, something that has been observed previously [Stevens and Wilroy, 1988].

Some anomalies were more prominent in one group. Of the major anomalies, many were more common in affected males in the XLOS families, including hypospadias, seen in 9/10 males in XLOS families versus 5/16 in the ADOS families. Imperforate anus was seen in 4/10 males from XLOS families, and in none of the ADOS families. However, imperforate anus has been seen in families with male-to-male transmission [Tolmie et al., 1987]; thus, is not exclusive to the XLOS families. Dysphagia was seen more commonly in the XLOS families (7/9 males and 3/13 females) than in ADOS (3/13 affected males and 1/8 females). Structural laryngotracheal abnormalities were found with similar frequency in the two groups. However, posterior pharyngeal clefts were seen only in XLOS families (individual IV-1 in family 5 and II-1 and III-2 in family 11). Furthermore, they have not been reported in a family with male-to-

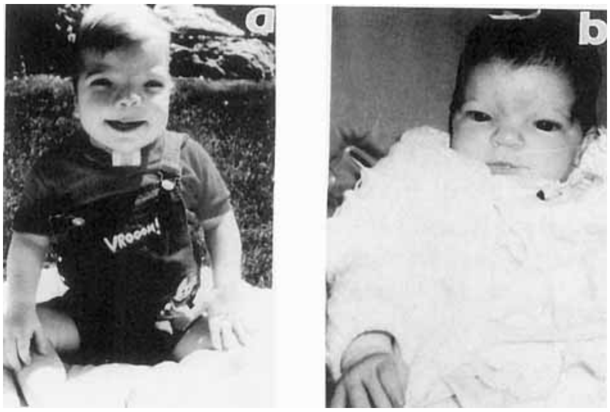

Figure 5a. Individual IV-1 from family 5. He manifests hypertelorism, agenesis of corpus callosum, cleft lip and palate, a thin upper lip with a smooth vermilion border, anteverted nares, laryngotracheal defect, hypospadias, and developmental delay. (5b) Individual IV-2, the sister of IV-1. She manifests hypertelorism, a broad and flat nasal bridge, and a thin upper lip with a smooth vermilion border.

Figure 6. Individual III-2, the mother of individuals IV-1 and IV-2 in family 5. She manifests hypertelorism only.

male transmission. Therefore, this anomaly may be specific to XLOS.

Developmental delay was frequent in ADOS, seen in approximately 25% of affected females and males, but in only one male from an XLOS family. This is in marked contrast to the literature, in which developmental delay was seen in 36 of 60 males, and in 17 of 35 females.

Of the minor craniofacial anomalies, anteverted nares are a trait that can differentiate XLOS from ADOS families. While this manifestation was seen in 4/6 affected males and 4/13 carrier females in XLOS families, it was not seen at all in ADOS families (0/20 total). Other minor manifestations, while seen more commonly in one group, were not as exclusive, and could be found in either group. A broad and prominent forehead was seen in nearly all affected individuals in ADOS families (11/13 males, 7/9 females), but was also seen in 7/8 affected males and 4/12 carrier females in XLOS families.

As expected, in the XLOS families, carrier females manifested a lower number of anomalies than affected males, including cleft lip and palate (0 in 14 carrier females compared to 3 in 7 affected males), laryngotracheal structural abnormality (1/8 vs. 3/4), dysphagia (3/13 vs. 7/9), and imperforate/ectopic anus (0/12 vs. 4/10).

Females carrying the OS allele also manifested a lower number of minor findings than affected males, including a broad, prominent forehead (4/12 vs. 7/8), anteverted

nares (4/13 vs. 4/6), and minor ear anomalies (2/13 vs. 7/7).

In contrast, the difference in phenotypic severity between males and females was less pronounced in ADOS families. Of the major anomalies, cleft lip and palate were seen more often in affected females than in affected males in ADOS families (2/7 vs. 3/15). The remaining anomalies were seen in approximately equal frequency, including laryngotracheal structural defect (2/13 vs. 1/7), dysphagia (3/13 vs. 1/8), and developmental delay (4/16 vs. 2/9). Some minor manifestations were seen less commonly in affected females, such as a broad nasal bridge (2/7 vs. 10/14), and minor ear anomalies (2/7 vs. 6/12), while the remainder were seen in approximately equal proportions.

Figure 7. Individual II-1, from family 12. He manifests hypertelorism, agenesis of the corpus callosum, a flat nasal bridge, a thin upper lip with a smooth vermilion border, tetralogy of Fallot, severe dysphagia (requiring gastrostomy), undescended testicles, and developmental delay.

Comparison of Study Patients and Those From the Literature

Most individuals who were found to carry the OS gene by linkage analysis were mildly affected, usually with only minor craniofacial manifestations. Hypertelorism was found at approximately the same frequency in the study families as those in the literature (92% in males, 93% in females). Except for males in the X-linked families, who had a 90% rate of hypospadias (9/10), other serious anomalies, such as congenital heart defect (26 of 71 patients from the literature versus 2 of 46 patients in this study), imperforate anus (32/103 vs. 4/47), and developmental delay (53/95 vs. 7/43) were seen in the study families at frequencies much lower than what has been previously reported. In addition, the incidence determined from the literature reports for other major anomalies such as cleft lip and palate and laryngotracheal structural abnormality also exceeded that observed in our study families. This may be due to ascertainment bias toward reporting of more severely affected individuals with incomplete evaluation of more distant relatives.

DISCUSSION

OS was first described in 1969 as two separate entities, the BBB syndrome [Christian et al., 1969; Opitz et al., 1969a], and the G syndrome [Opitz et al., 1969b]. While these conditions shared the traits of hypertelorism and hypospadias, they were thought to be distinct because of the presence of laryngotracheal clefting, esophageal dysmotility, and imperforate anus in the G family, and mental retardation and cleft lip and palate, seen only in the BBB families. However, subsequent reports of families in which the findings of both BBB and G syndrome

segregated within a single kindred suggested that they were a single clinical entity [Cordero and Holmes, 1978; Cappa et al., 1987; Sedano and Gorlin, 1988].

While it became evident that the G and BBB syndromes were actually the same clinical condition, the inheritance of the disorder could not be defined. The pedigrees in the initial reports were compatible with either XLOS or autosomal dominant inheritance. X-linked inheritance was supported by the observation that males seemed to be more severely affected than females, with some obligate carriers even appearing phenotypically normal [Opitz, 1987; Stevens and Wilroy, 1988]. However, as subsequent reports documented families with male-to-male transmission of the OS phenotype [Funderburk and Stewart, 1978; Farndon and Donnai, 1983; Chemke et al., 1984; Tolmie et al., 1987; Wilson and Oliver, 1988], autosomal dominant inheritance became more accepted [Opitz, 1987]. However, our recent finding of heterogeneity [Robin et al., 1995] has now caused a reevaluation of the genetics of OS.

Wide clinical variability, ranging from neonatal lethality to an asymptomatic form, has been well-described in OS, often causing difficulty in making this diagnosis [Opitz, 1987]. As is shown in this study, individuals carrying the affected allele may manifest few signs of OS, with our patients less affected than those described in the literature. For example, cleft lip and palate has been reported in 49% of affected males and 15% of affected females compared with 43% of affected males and 0 affected females in XLOS families, and 20% of affected males and 29% of affected females in ADOS families. In addition, non-penetrance was observed in both groups. This confirms that the wide variability in OS includes clinically normal gene carriers [Opitz, 1987; Stevens and Wilroy, 1988]. Therefore, in most cases, affected individuals manifest few signs of the disorder, most commonly with only hypertelorism and a broad, prominent forehead. This was true in both XLOS and ADOS.

In both groups, the classic craniofacial signs of OS were apparent, including wide-spaced eyes, flat nasal bridge, thin upper lip, and minor ear anomalies. Few manifestations were found to occur more frequently in one group, and only anteverted nares was an exclusive finding limited to XLOS families. In ADOS families, no definitive exclusive craniofacial anomaly was seen. However, the presence of a broad, prominent forehead and overall "coarser" facial appearance was much more common in this group.

The major malformations common in OS were also represented in both groups, including hypospadias, cleft lip/palate, congenital heart defect, swallowing difficulties, and developmental delay. It is interesting that laryngotracheal clefting in families 5 and 11, and imperforate anus in families 3 and 11, were found only in XLOS families. A review has established the occurrence of imperforate anus [Tolmie et al., 1987] and pharyngeal abnormalities [Farndon and Donnai, 1983; Stoll et al., 1985; Tolmie et al., 1987] in families with male-to-male transmission. However, in none of these instances was the pharyngeal abnormality the laryngotracheal cleft described in the original reports [Opitz et al., 1969a]. This may then be another specific finding for the XLOS phenotype.

While major anomalies were seen in both groups of OS families, males with XLOS were the most severely affected, manifesting one or more anomaly much more frequently than affected individuals in any other subgroup. Notably, 7/9 affected XLOS males had dysphagia/aspiration/gastroesophageal reflux, and 9/10 had hypospadias. Despite disparities in the rate of observed anomalies, comparison of

the phenotypes in the two groups did not provide a unique manifestation differentiating XLOS from ADOS. That is not to say that the phenotypes are indistinguishable. The presence of anteverted nares or the classic laryngotracheal cleft is suggestive of X-linkage. Similarly, the presence of a broad forehead with a coarse facial appearance would suggest that the family is 22-linked. But it is important to note that these clinical differences are not conclusive, and it will only be after more families are studied at a molecular level that more definitive distinctions can be drawn.

Comparison of XLOS to Other Xp22 Syndromes

The finding that a subset of families with OS maps to Xp22 makes OS the third craniofacial disorder mapping to this region. Craniofrontonasal syndrome (CFNS) is an X-linked disorder of hypertelorism, broad forehead, craniofacial asymmetry, a broad and often grooved nasal tip, craniosynostosis, and a variety of limb and digital anomalies [Cohen, 1979]. It is thought to map to Xp22 based on the finding of a patient with CFNS and an Xp22-pter deletion [McPherson et al., 1991]. Manifestations of CFNS, such as hypertelorism, craniofacial asymmetry, a broad forehead, and a grooved nasal tip are commonly seen in OS [Opitz, 1987].

In addition, a novel multiple congenital anomaly syndrome was reported in a family where two sisters had 3 affected boys with hypertelorism, a broad forehead, a long philtrum, a thin upper lip, anteverted ears, intrauterine growth retardation, microcephaly, and severe neurologic impairment [Wittwer et al., 1994]. Linkage analysis localized the gene in this family to Xp22.

The finding that three different conditions with similar craniofacial findings map to Xp22 is interesting, as 3 zinc finger genes (ZFN) are located near Xp22: ZFN41 [Franzè et al., 1991], ZFN81 [Marino et al., 1993], and ZFX [Page et al., 1990]. Some zinc finger genes have been shown to be important in craniofacial development, such as *GLI3*, the gene for Greig cephalopolysyndactyly [Vortkamp et al., 1991]. Therefore, these ZFN genes are attractive candidates for these craniofacial syndromes. Alternatively, these 3 conditions could represent different phenotypic expressions of abnormalities in the same gene.

Comparison of ADOS to the del (22)(q11) Syndromes

The finding that half of our families studied were linked to markers mapping to 22q was surprising, as this region is also the locus for the deletion 22q11.2 syndrome, which includes velocardiofacial syndrome (VCFS), DiGeorge anomaly (DGA), and conotruncal anomaly-face syndrome (CTAF) [Driscoll et al., 1992a; Driscoll et al., 1992b; Burn et al., 1993]. In addition, some cases of ADOS have been shown to be associated with deletions of 22q11.2. These were patients with findings of both DG/VCF (vascular ring and hypocalcemia), and OS (hypertelorism, hypospadias), who were deleted for 22q11.2 [McDonald-McGinn et al., 1995].

Clinically, there is some overlap of the types of congenital heart disease seen in the two entities. In DG/VCF, conoventricular congenital heart defects are common, including interrupted aortic arch, coarctation of the aorta (CoA), ventriculoseptal defects (VSD), tetralogy of Fallot (TOF), vascular rings [Goldmutz et al., 1993], and pulmonary stenosis (PS) [Lipson et al., 1991; Seaver et al., 1994]. Similar cardiac

TABLE II. Cardiac Defects Seen in Reported Cases of Opitz Syndrome

Atrial septal defect	2
Ventriculoseptal defect	5
Patent ductus arteriosus	11
Vascular ring	1
Tetralogy of Fallot	3
Coarctation of the aorta	2
Complex congenital heart defect	4

defects are also seen in OS (Table II), including PS and VSD [Stoll et al., 1985] and aortic stenosis, PS, and CoA [Farndon and Donnai, 1983] in families with male-to-male transmission. However, the most common congenital heart disease in OS is patent ductus arteriosus (PDA), a type of heart lesion not common in the DG/VCF spectrum. In addition, some prominent manifestations of OS, such as hypertelorism, cleft lip, laryngotracheal abnormalities, swallowing dysfunction, and hypospadias, are not as commonly seen in DG/VCF. Furthermore, learning disabilities are seen in nearly every patient with DG/VCF [Goldberg et al., 1993], but were seen in only 6/25 patients in ADOS families.

Based on these clinical data, it appears that OS is a condition clinically distinct from DG/VCF. However, future research will determine if this distinction is true at the molecular level as well. Further work toward sublocalizing the OS gene on 22q, as well as the gene on Xp22, is currently ongoing. It is interesting to note that 22q11.2 contains 4 zinc finger genes: ZFN69, ZFN70, ZFN71, and ZFN74 [Aubry et al., 1992]. While a role for these genes in development is not currently known, they are attractive candidate genes for ADOS.

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